

WHAT IS CLAIMED IS:

1. Method for the production of recombinant DNA-derived tissue plasminogen activator (tPA), a tPA variant, a Kringle 2 Serine protease molecule (K2S) or a K2S variant in prokaryotic cells, wherein said tPA, tPA variant, K2S molecule or K2S variant is secreted extracellularly as an active and correctly folded protein, characterized in that the prokaryotic cell contains and expresses a vector comprising the DNA coding for said tPA, tPA variant, K2S molecule or K2S variant operably linked to the DNA coding for the signal peptide OmpA or a functional derivative thereof.

2. Method according to claim 1, characterised in that said the prokaryotic cell contains and expresses a vector comprising the DNA coding for said tPA, tPA variant, K2S molecule or K2S variant operably linked to the DNA coding for the signal peptide OmpA which is operably linked to the nucleic acid molecule defined by the sequence TCTGAGGGAAACAGTGAC (SEQ ID NO:1) or a functional derivative thereof.

3. Method according to claim 1 or 2, characterised in that the prokaryotic cell is *E. coli*.

4. Method according to one of claims 1 to 3, characterised in that the the following steps are carried out:

a) the DNA encoding the tPA, tPA variant, K2S molecule or K2S variant is amplified by PCR;

b) the PCR product is purified;

c) said PCR product is inserted into a vector comprising the DNA coding for OmpA signal peptide and the DNA coding for gpIII in such a way that said PCR product is operably linked upstream to the DNA coding for the OmpA signal sequence and linked downstream to the DNA coding for gpIII of said vector;

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- d) that a stop codon is inserted between said tPA, tPA variant, K2S molecule or K2S variant and gpIII;
- e) said vector is expressed by the prokaryotic cell;
- f) the tPA, tPA variant, K2S molecule or K2S variant is purified.

5. Method according to one of claims 1 to 4, characterised in that the vector is a phagemid vector comprising the DNA coding for OmpA signal peptide and the DNA coding for gpIII.

6. Method according to one of claims 1 to 5, characterised in that the vector is the pComb3HSS phagemid.

7. Method according to one of claims 1 to 6, characterised in that the DNA Sequence of OmpA linked upstream to K2S comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCCGAGGCGGCTCTGAGGGAAACAGTGACTGCTACTT
TGGAATGGGTCAGCCTACCGTGGCACGCACAGCCTCACCGAGTCG
GGTGCCTCCTGCCTCCCGTGGAATTCCATGATCCTGATAGGCAAGG
TTTACACAGCACAGAACCCAGTGCCCAGGCACTGGGCCTGGGCA
AACATAATTACTGCCGGAATCCTGATGGGGATGCCAAGCCCTGGTG
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT
GCCCTCCTGCTCCACCTGCGGCCTGAGACAGTACAGCCAGCCTCAG
TTTCGCATCAAAGGAGGGCTCTTCGCCGACATCGCCTCCCACCCCT
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTGCCCCGGAGAGC
GGTTCCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCTCT
GCCGCCCACTGCTTCCAGGAGAGGTTTCCGCCCCACCACCTGACGG
TGATCTTGGGCAGAACATAACCGGTGGTCCCTGGCGAGGAGGAGC
AGAAATTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA

Sub (a)
TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT
TCGTCCCGCTGTGCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC
TCCCCCGGCGGACCTGCAGCTGCCGGACTGGACGGAGTGTGAGCT
CTCCGGCTACGGCAAGCATGAGGCCTTGTCTCCTTTCTATTTCGGAG
CGGCTGAAGGAGGCTCATGTCAGACTGTACCCATCCAGCCGCTGCA
CATCACAACATTTACTTAACAGAACAGTCACCGACAACATGCTGTG
TGCTGGAGACACTCGGAGCGGCGGGCCCCAGGCAAACCTTGACGA
CGCCTGCCAGGGCGATTTCGGGAGGCCCCCTGGTGTGTCTGAACGAT
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGGCCTGGGCTGTG
GACAGAAGGATGTCCCCGGGTGTGTACACAAAGGTTACCAACTACCT
AGACTGGATTTCGTGACAACATGCGACCG (SEQ ID NO:2)

8. Method according to one of claims 1 to 7, characterised in that the DNA Sequence of OmpA comprises the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:3)

9. Method according to one of claims 1 to 8, characterised in that the DNA Sequence of OmpA consists of the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:3)

10. Method according to one of claims 1 to 9, characterised in that the DNA of the tPA, tPA variant, K2S molecule or K2S variant is preceded by a lac promotor and/or a ribosomal binding site.

11. Method according to one of claims 1 to 10, characterised in that the DNA coding for the tPA, tPA variant, K2S molecule or K2S variant is selected from the group of DNA molecules coding for at least 90% of the amino acids 87 – 527, 174 – 527, 180 – 527 or 220 – 527 of the human tissue plasminogen activator protein.

12. Method according to one of claims 5 to 11, characterised in that the DNA Sequence of K2S comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC
AGTGCCCAGGCACTGGGCCTGGGCAAACATAATTACTGCCGGAATC
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGCTC
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTTGCCA
AGCACAGGAGGTCGCCCCGAGAGCGGTTCTGTGCGGGGGGCATAC
TCATCAGCTCCTGCTGGATTCTCTCTGCCGCCCCTGCTTCCAGGAG
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATACC
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT
ACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT
TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAG
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG
AGGCCTTGTCTCCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC
GGCGGGCCCCAGGCAAACCTGCACGACGCCTGCCAGGGCGATTTCG
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTTCGTGACAA
CATGCGACCGTGA (SEQ ID NO:4).

13. Method according to one of claims 5 to 12, characterised in that the DNA Sequence of K2S consists of the following sequence:

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TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC
AGTGCCCAGGCACTGGGCCTGGGCAAACATAATTACTGCCGGAATC
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGGCTC
TTCGCCGACATCGCCTCCACCCCTGGCAGGCTGCCATCTTTGCCA
AGCACAGGAGGTCGCCCGGAGAGCGGTTCTGTGCGGGGGGCATAC
TCATCAGCTCCTGCTGGATTCTCTCTGCCGCCCACTGCTTCCAGGAG
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATACC
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT
ACATTGTCCATAAGGAATTTCGATGATGACACTTACGACAATGACAT
TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAG
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG
AGGCCTTGTCTCCTTTCTATTTCGAGCGGCTGAAGGAGGCTCATGT
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC
GGCGGGCCCCAGGCAAACCTGCACGACGCCTGCCAGGGCGATTTCG
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTTCGTGACAA
CATGCGACCGTGA (SEQ ID NO:4).

14. DNA molecule characterized in that it is coding for:

a) the OmpA protein or a functional derivative thereof operably linked to

b) a DNA molecule coding for a polypeptide containing the kringle 2 domain and the serine protease domain of tissue plasminogen activator protein.

15. DNA molecule according to claim 14, characterized in that said DNA sequence comprises the following sequence or a functional variant thereof or a variant due to the degenerate nucleotide code:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCCAGGCGGCCTCTGAGGGAAACAGTGACTGCTACTT
TGGGAATGGGTCAGCCTACCGTGGCACGCACAGCCTCACCGAGTCG
GGTGCCTCCTGCCTCCCGTGGGAATTCCATGATCCTGATAGGCAAGG
TTTACACAGCACAGAACCCCAGTGCCCAGGCACTGGGCCTGGGCA
AACATAATTACTGCCGGAATCCTGATGGGGATGCCAAGCCCTGGTG
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT
GCCCTCCTGCTCCACCTGCGGCCTGAGACAGTACAGCCAGCCTCAG
TTTCGCATCAAAGGAGGGCTCTTCGCCGACATCGCCTCCCACCCCT
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTCGCCCGGAGAGC
GGTTCCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCTCT
GCCGCCCCTGCTTCCAGGAGAGGTTTCCGCCCCACCACCTGACGG
TGATCTTGGGCAGAACATAACCGGTGGTCCCTGGCGAGGAGGAGC
AGAAATTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA
TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT
TCGTCCCGCTGTGCCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC
TTCCCCCGGCGGACCTGCAGCTGCCGACTGGACGGAGTGTGAGCT
CTCCGGCTACGGCAAGCATGAGGCCTTGTCTCCTTTCTATTTCGGAG
CGGCTGAAGGAGGCTCATGTCAGACTGTACCCATCCAGCCGCTGCA
CATCACAACATTTACTTAACAGAACAGTCACCGACAACATGCTGTG
TGCTGGAGACACTCGGAGCGGCGGGCCCCAGGCAAACCTTGCACGA
CGCCTGCCAGGGCGATTTCGGGAGGCCCCCTGGTGTGTCTGAACGAT
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGGCCTGGGCTGTG
GACAGAAGGATGTCCCGGGTGTGTACACAAAGGTTACCAACTACCT
AGACTGGATTTCGTGACAACATGCGACCG (SEQ ID NO:5).

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Seq ID NO: 5

16. DNA molecule according to claim 14 or 15, characterized in that said DNA sequence consists of the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGCCCCAGGCGGCCTCTGAGGGAAACAGTGACTGCTACTT
TGGGAATGGGTCAGCCTACCGTGGCACGCACAGCCTCACCGAGTCG
GGTGCCTCCTGCCTCCCGTGGGAATTCCATGATCCTGATAGGCAAGG
TTTACACAGCACAGAAACCCAGTGCCCAGGCACTGGGCCTGGGCA
AACATAATTACTGCCGGAATCCTGATGGGGATGCCAAGCCCTGGTG
CCACGTGCTGAAGAACCGCAGGCTGACGTGGGAGTACTGTGATGT
GCCCTCCTGCTCCACCTGCGGCCTGAGACAGTACAGCCAGCCTCAG
TTTCGCATCAAAGGAGGGCTCTTCGCCGACATCGCCTCCCACCCCT
GGCAGGCTGCCATCTTTGCCAAGCACAGGAGGTGCCCCGGAGAGC
GGTTCCTGTGCGGGGGCATACTCATCAGCTCCTGCTGGATTCTCTCT
GCCGCCCACTGCTTCCAGGAGAGGTTTCCGCCCCACCACCTGACGG
TGATCTTGGGCAGAACATAACCGGGTGGTCCCTGGCGAGGAGGAGC
AGAAATTTGAAGTCGAAAAATACATTGTCCATAAGGAATTCGATGA
TGACACTTACGACAATGACATTGCGCTGCTGCAGCTGAAATCGGAT
TCGTCCCGCTGTGCCCAGGAGAGCAGCGTGGTCCGCACTGTGTGCC
TTCCCCCGGCGGACCTGCAGCTGCCGGACTGGACGGAGTGTGAGCT
CTCCGGCTACGGCAAGCATGAGGCCTTGTCTCCTTTCTATTTCGGAG
CGGCTGAAGGAGGCTCATGTGAGACTGTACCCATCCAGCCGCTGCA
CATCACAACATTTACTTAACAGAACAGTCACCGACAACATGCTGTG
TGCTGGAGACACTCGGAGCGGCGGGCCCCAGGCAAACCTTGCACGA
CGCCTGCCAGGGCGATTTCGGGAGGCCCCCTGGTGTGTCTGAACGAT
GGCCGCATGACTTTGGTGGGCATCATCAGCTGGGGCCTGGGCTGTG
GACAGAAGGATGTCCCGGGTGTGTACACAAAGGTTACCAACTACCT
AGACTGGATTTCGTGACAACATGCGACCG (SEQ ID NO:5).

17. DNA molecule according to one of claims 14 to 16, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 87 – 527 of the human tissue plasminogen activator protein.

18. DNA molecule according to one of claims 14 to 17, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 174 – 527 of the human tissue plasminogen activator protein.

19. DNA molecule according to any one of claims 14 to 18, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 180 – 527 of the human tissue plasminogen activator protein.

20. DNA molecule according to any one of claims 14 to 19, characterized in that said DNA sequence b) is coding for at least 90% of the amino acids 220 – 527 of the human tissue plasminogen activator protein.

21. DNA molecule according to any one of claims 14 to 20, characterized in that said DNA sequence a) is hybridizing under stringent conditions to the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:6).

22. DNA molecule according to any one of claims 14 to 21, characterized in that said DNA sequence a) consists of the following sequence:

ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCG
CTACCGTGGCCCAGGCGGCC (SEQ ID NO:6).

23. DNA molecule according to any one of claims 14 to 22, characterized in that said DNA sequence b) is hybridizing under stringent conditions to the following sequence:

TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC

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AGTGCCCAGGCACTGGGCCTGGGCAAACATAATTACTGCCGGAATC
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG
CCTGAGACAGTACAGCCAGCCTCAGTTTCGCATCAAAGGAGGGCTC
TTCGCCGACATCGCCTCCCACCCCTGGCAGGCTGCCATCTTTGCCA
AGCACAGGAGGTGCGCCCGGAGAGCGGTTCTGTGCGGGGGGCATAC
TCATCAGCTCCTGCTGGATTCTCTCTGCGCCCACTGCTTCCAGGAG
AGGTTTCCGCCCCACCACCTGACGGTGATCTTGGGCAGAACATACC
GGGTGGTCCCTGGCGAGGAGGAGCAGAAATTTGAAGTCGAAAAAT
ACATTGTCCATAAGGAATTCGATGATGACACTTACGACAATGACAT
TGCGCTGCTGCAGCTGAAATCGGATTCGTCCCGCTGTGCCCAGGAG
AGCAGCGTGGTCCGCACTGTGTGCCTTCCCCCGGCGGACCTGCAGC
TGCCGGACTGGACGGAGTGTGAGCTCTCCGGCTACGGCAAGCATG
AGGCCTTGCTCTCCTTTCTATTTCGGAGCGGCTGAAGGAGGCTCATGT
CAGACTGTACCCATCCAGCCGCTGCACATCACAACATTTACTTAAC
AGAACAGTCACCGACAACATGCTGTGTGCTGGAGACACTCGGAGC
GGCGGGCCCCAGGCAAACCTTGACGACGCCTGCCAGGGCGATTTCG
GGAGGCCCCCTGGTGTGTCTGAACGATGGCCGCATGACTTTGGTGG
GCATCATCAGCTGGGGCCTGGGCTGTGGACAGAAGGATGTCCCGG
GTGTGTACACAAAGGTTACCAACTACCTAGACTGGATTTCGTGACAA
CATGCGACCGTGA (SEQ ID NO:7).

24. DNA molecule according to any one of claims 14 to 23, characterized in that said DNA sequence b) consists of the following sequence:

TCTGAGGGAAACAGTGACTGCTACTTTGGGAATGGGTCAGCCTACC
GTGGCACGCACAGCCTCACCGAGTCGGGTGCCTCCTGCCTCCCGTG
GAATTCCATGATCCTGATAGGCAAGGTTTACACAGCACAGAACCCC
AGTGCCCAGGCACTGGGCCTGGGCAAACATAATTACTGCCGGAATC
CTGATGGGGATGCCAAGCCCTGGTGCCACGTGCTGAAGAACCGCA
GGCTGACGTGGGAGTACTGTGATGTGCCCTCCTGCTCCACCTGCGG

MKKTAIAIAVALAGFATVAQAASEGNSDCYFGNGSAYRGTHSLTESG
 ASCLPWNSMILIGKVYTAQNPSAQUALGLGKHNYCRNPDGDAKPWCH
 VLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGFLADIASHPWQA
 AIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHHLTIVILGRY
 RVVPGEEEQKFEVEKYIVHKEFDDDTYDNDIALQLKSDSSRCAQESS
 VVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERLKEAHVRLYP
 SSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSSGGPLVC

LNDGRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNM RPG
(SEQ ID NO:8).

26. Fusion protein of OmpA and K2S according to claim 25, characterised in that it consists of a protein characterized by the following amino acid sequence:

MKKTAIAIAVALAGFATVAQAASEGNSDCYFGNGSAYRGTHSLTESG
ASCLPWNSMILIGKVYTAQNPSAQALGLGKHNYCRNPDGDAKPWCH
VLKNRRLTWEYCDVPSCSTCGLRQYSQPQFRIKGGLFADIASHPWQA
AIFAKHRRSPGERFLCGGILISSCWILSAAHCFQERFPPHHLTIVLGRTY
RVVPGEEEQKFEVEKYIVHKEFDDDTYDNDIALQLKSDSSRCAQESS
VVRTVCLPPADLQLPDWTECELSGYGKHEALSPFYSERLKEAHVRLYP
SSRCTSQHLLNRTVTDNMLCAGDTRSGGPQANLHDACQGDSSGGLVC
LNDGRMTLVGIISWGLGCGQKDVPGVYTKVTNYLDWIRDNM RPG
(SEQ ID NO:8).

27. K2S protein, characterised in that it comprises a protein defined by the sequence SEGN (SEQ ID NO:9) and a or a variant or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative, a fusion protein or a glycosylation variant thereof.

28. K2S protein according to claim 27, characterised in that it comprises a protein defined by the sequence SEGNSD (SEQ ID NO:10) and a or a variant or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative, a fusion protein or a glycosylation variant thereof.

29. K2S protein according to claim 28 or 29, characterised in that it comprises a protein characterized by the following amino acid sequence or a fragment, a functional variant, an allelic variant, a subunit, a chemical derivative or a glycosylation variant thereof:

Sub 63
SEGNSDCYFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSA
QALGLGKHNYCRNPDGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLR
QYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWI
LSAAHCFQERFPPHLLTVILGR TYRVVPGE EEEQKFEVEKYIVHKEFDD
DTYDNDIAL LQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSG
YGKHEALSPFYSERLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGD
TRSGGPQANLHDACQGDSGGPLVCLNDGRMTLVGIISWGLGCGQKD
VPGVYTKVTNYLDWIRDNM RP* (SEQ ID NO:11).

30. K2S according to any one of claims 27 to 30, characterised in that it consists of a protein characterized by the following amino acid sequence:

SEGNSDCYFGNGSAYRGTHSLTESGASCLPWNSMILIGKVYTAQNPSA
QALGLGKHNYCRNPDGDAKPWCHVLKNRRLTWEYCDVPSCSTCGLR
QYSQPQFRIKGGLFADIASHPWQAAIFAKHRRSPGERFLCGGILISSCWI
LSAAHCFQERFPPHLLTVILGR TYRVVPGE EEEQKFEVEKYIVHKEFDD
DTYDNDIAL LQLKSDSSRCAQESSVVRTVCLPPADLQLPDWTECELSG
YGKHEALSPFYSERLKEAHVRLYPSSRCTSQHLLNRTVTDNMLCAGD
TRSGGPQANLHDACQGDSGGPLVCLNDGRMTLVGIISWGLGCGQKD
VPGVYTKVTNYLDWIRDNM RP* (SEQ ID NO:11).

31. A vector containing a DNA sequence according to any one of claims 14 to 24.

32. A vector according to claim 31, wherein said DNA sequence is preceeded by a lac promoter and a ribosomal binding site.

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33. The vector pComb3HSS containing a DNA according to any one of claims 14 to 24, wherein the expression of the gp III protein is suppressed or inhibited by deleting the DNA molecule encoding said gp III protein or by a stop codon between the gene coding for a a polypeptide

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containing the kringle 2 domain and the serine protease domain of tissue plasminogen activator protein and the protein III gene.

34. A prokaryotic host cell comprising a DNA molecule according to any one of claims 14 to 24.

35. A prokaryotic host cell comprising a vector according to any one of claims 31 to 33.

36. An *E. coli* host cell comprising a DNA molecule according to any one of claims 14 to 24.

37. An *E. coli* host cell comprising a vector according to any one of claims 31 to 33.

38. Use of a DNA molecule according to any one of claims 14 to 24 or of a vector according to any one of claims 31 to 33 or a host cell according to any one of claims 34 to 37 in a method for the production of a polypeptide having the activity of tissue plasminogen activator.

39. Use according to claim 38, wherein said method is a method according to any one of claims 1 to 13.